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Abstract: PURPOSE: : To assess the efficacy and safety of using simultaneous integrated boost intensity-modulated radiotherapy (SIB-IMRT) to treat nasopharyngeal cancer (NPC) in a Caucasian cohort. Outcome was analyzed with respect to dose-volume histogram (DVH) values. PATIENTS AND METHODS: : Between 03/2002 and 01/2008, 39 NPC patients underwent SIB-IMRT (37 Caucasians; 31 males; mean age 53 years [16-78 years]). 41% presented with WHO (World Health Organization) type 1 unfavorable histology, 85% with stage III/IV disease. 19 patients had total gross tumor volume (GTV) 16-70 cm3 (mean 36 cm3), while 16 had GTV > 70 cm3 (73-217 cm3; mean 115 cm3). All patients with stage II-IV disease received concomitant cisplatin. The prescribed SIB dose delivered to the planning target volume (PTV) was 70 Gy (2.00 Gy/fraction) in 17, 69.6 Gy (2.11 Gy/fraction) in 19, and 66 Gy (2.20 Gy/fraction) in three patients. RESULTS: : 3-year local relapse-free, nodal relapse-free, distant metastases-free, disease-free rates and overall survival were 86%, 89%, 85%, 72%, and 85% (median follow-up 30 months [8-71 months]). Histology was a significant prognostic factor concerning overall survival, with worst prognosis in WHO type 1 compared to type 2/3 (75% vs. 93%; p = 0.03). There was a trend in favor of WHO type 2/3 regarding local control (74% vs. 94%; p = 0.052). The PTV DVHs showed a slight left shift compared to reported series. Three patients developed grade 3 late effects (xerostomia [n = 2], dysphagia [n = 1], hearing loss [n = 1]). CONCLUSION: : In comparison with predominantly Asian NPC IMRT series in the literature, chemo-IMRT in the own Caucasian cohort, characterized by less radioresponsive WHO type 1, was equally effective. Treatment tolerance was excellent.

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Simultaneous Integrated Boost Intensity-Modulated Radiotherapy (SIB-IMRT) in Nasopharyngeal Cancer

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Purpose: To assess the efficacy and safety of using simultaneous integrated boost intensity-modulated radiotherapy (SIB-IMRT) to treat nasopharyngeal cancer (NPC) in a Caucasian cohort. Outcome was analyzed with respect to dose-volume histogram (DVH) values.

Patients and Methods: Between 03/2002 and 01/2008, 39 NPC patients underwent SIB-IMRT (37 Caucasians; 31 males; mean age 53 years [16–78 years]). 41% presented with WHO (World Health Organization) type 1 unfavorable histology, 85% with stage III/IV disease. 19 patients had total gross tumor volume (GTV) 16–70 cm^3 (mean 36 cm^3), while 16 had GTV > 70 cm^3 (73–217 cm^3; mean 115 cm3). All patients with stage II–IV disease received concomitant cisplatin.
The prescribed SIB dose delivered to the planning target volume (PTV) was 70 Gy (2.00 Gy/fraction) in 17, 69.6 Gy (2.11 Gy/fraction) in 19, and 66 Gy (2.20 Gy/fraction) in three patients.

Results: 3-year local relapse-free, nodal relapse-free, distant metastases-free, disease-free rates and overall survival were 86%, 89%, 85%, 72%, and 85% (median follow-up 30 months [8–71 months]). Histology was a significant prognostic factor concerning overall survival, with worst prognosis in WHO type 1 compared to type 2/3 (75% vs. 93%; p = 0.03). There was a trend in favor of WHO type 2/3 regarding local control (74% vs. 94%; p = 0.052). The PTV DVHs showed a slight left shift compared to reported series. Three patients developed grade 3 late effects (xerostomia [n = 2], dysphagia [n = 1], hearing loss [n = 1]).

Conclusion: In comparison with predominantly Asian NPC IMRT series in the literature, chemo-IMRT in the own Caucasian cohort, characterized by less radioresponsive WHO type 1, was equally effective. Treatment tolerance was excellent.

Key Words: Nasopharyngeal carcinoma in Caucasians · Intensity-modulated radiotherapy · Simultaneous integrated boost

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Intensitätsmodulierte Radiotherapie mit simultan integriertem Boost (SIB-IMRT) beim Nasopharynxkarzinom

Ziel: Es wurden Wirksamkeit und Effektivität der intensitätsmodulierten Radiotherapie mit simultan integriertem Boost (SIB-IMRT) beim Nasopharynxkarzinom (NPC) untersucht. Die Resultate werden unter Berücksichtigung der Dosis-Volumen-Histogramm-(DVH-)Werte diskutiert.

Patienten und Methodik: Zwischen 03/2002 und 01/2008 wurden 39 NPC-Patienten mit SIB-IMRT behandelt (37 Kaukasier; 31 Männer; im Mittel 53 Jahre [16–78 Jahre]). 41% hatten eine ungünstige WHO-Typ-1-Histologie, 85% waren im Stadium III/IV. 19 Patienten wiesen ein Gesamttumorvolumen (GTV) von 16–70 cm^3 (Mittelwert 36 cm^3), 16 Patienten von > 70 cm^3 (73–217 cm^3; Mittelwert 115 cm^3) auf. Alle Patienten im Stadium II–IV erhielten simultan Cisplatin.
Die SIB-Dosis auf das Boost-Planungszielvolumen (PTV) betrug 70 Gy (2,00 Gy/Sitzung) bei 17, 69,6 Gy (2,11 Gy/Sitzung) bei 19 und 66 Gy (2,20 Gy/Sitzung) bei drei Patienten.

Ergebnisse: Mit einer mittleren Verlaufsbeobachtung von 30 Monaten (8–71 Monate) lagen die 3-Jahres-Überlebensraten für die Lokal-, Nodal- und Fernkontrolle bei 86%, 89% und 85%, das krankheitsfreie Überleben und das Gesamtüberleben betrugen 72% und 85%. Die Histologie war ein signifikanter prognostischer Faktor hinsichtlich des Gesamtüberlebens, mit ungünstigerer Prognose bei WHO-Typ-1-Histologie im Vergleich zu Typ 2/3 (75% vs. 93%; p = 0,03). Bezüglich der Lokalkontrolle zeigte sich ein Trend zugunsten Typ 2/3 (74% vs. 94%; p = 0,052). In den PTV-DVHs fand sich eine leichtgradige Linksverschiebung im Vergleich zu anderen Serien. Drei Patienten zeigten Grad-3-Spättoxizität (Xerostomie [n = 2], Dysphagie [n = 1], Schwerhörigkeit [n = 1]).

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Schlussfolgerung: Im Vergleich zur IMRT-Literatur mit großteils asiatischen Populationen fanden sich nach Chemo-IMRT bei der eigenen kaukasischen NPC-Kohorte mit großem Anteil an radioresistentem WHO-Typ 1 ähnliche Resultate. Die Therapietoleranz war ausgezeichnet.

Schlüsselwörter: Nasopharynxkarzinom und Kaukasier · Intensitätsmodulierte Radiotherapie · Simultan integrierter Boost

Introduction

Nasopharyngeal cancer (NPC) is highly prevalent in Asian populations, while it is rare among Caucasians [17, 44]. Historically, the local control for early stage reaches 80–90%, whereas T3–T4 tumors have a control rate of 30–65% [14, 25, 32]. Improvement in technical accuracy and radiotherapy delivery has been linked with improved tumor control [36].

Various methods have been used to improve local control by increasing the dose delivered, including brachytherapy [6, 37], stereotactic radiotherapy [13], three-dimensional conformal radiotherapy [39, 42] and intensity-modulated radiotherapy (IMRT) [3, 22, 40]. IMRT allows for the simultaneous delivery of different doses to different target volumes, representing an ideal technique for localized dose escalation [26, 31].

WHO (World Health Organization) histology type is regarded as an independent prognostic factor for survival in NPC, with less favorable prognosis in squamous WHO type 1 [5, 29]. Also, patients of Asian origin are considered to have improved survival when compared to non-Asians [2, 24].

Dose-volume histogram (DVH) comparison between institutions remains difficult, as there does not yet exist an international standardization regarding contouring definition, prescription dose, volume-related dose distribution and IMRT fractionation and dose normalization.

We evaluate the outcome and toxicity profile of chemo-SIB-(simultaneous integrated boost-)IMRT in our predominantly Caucasian collective characterized by a high proportion of unfavorable WHO type 1 histology. Results were analyzed with respect to the DVH values resulting from our SIB-IMRT dose definition.

Patients and Methods

Patient, Disease and Staging Characteristics

Between March 2002 and January 2008, 39 patients underwent IMRT for NPC at our department. All were staged using the 2002 American Joint Committee on Cancer (AJCC) criteria [9].

Pretreatment evaluation included complete history, physical examination, direct flexible fiberoptic endoscopy, magnetic resonance imaging (MRI) scans of the nasopharynx, skull base and neck, chest computed tomography (CT) or X-ray, laboratory studies, and dental evaluation. Most patients (> 90%) underwent fused CT-positron emission tomography (PET) initially.

Patient and disease characteristics are listed in Table 1. Mean age of the cohort was 53 years (16–78 years). TN staging is outlined in Table 2.

IMRT Planning

Patients were immobilized from head to shoulders with commercially available thermoplastic masks and an individually

Table 1. Patient and disease characteristics (n = 39). EBV: Epstein-Barr virus; ECOG: Eastern Cooperative Oncology Group; NA: not assessable; PS: performance status; tGTV: total gross tumor volume; WHO: World Health Organization.

Tabelle 1. Patienten- und Tumorcharakteristika (n = 39). EBV: Epstein-Barr-Virus; ECOG: Eastern Cooperative Oncology Group; NA: nicht angebbar; PS: Leistungstatus; tGTV: Gesamttumorvolumen; WHO: Weltgesundheitsorganisation.

Characteristics	Cases	
	n	(%)
Gender (male : female)	31 : 8	79 : 21
Ethnicity (Caucasian : Asian)	37 : 2	95 : 5
WHO/ECOG PS		
• PS 0	26	67
• PS 1	13	33
WHO histology		
• Type 1 (squamous)	16	41
• Type 2/3 (nonkeratinizing)	23	59
EBV		
• Positive	21	54
• Negative	4	10
• NA	14	36
Grade		
• G1	2	5
• G2	5	13
• G3	32	82
Stage III/IV	33	85
T3/4	22	56
tGTV (mean; range)		
• $\leq$ 15 cm^3	4 (12.5 cm^3; 11–13 cm^3)	10
• 16–70 cm^3	19 (36 cm^3; 17–63 cm^3)	49
• > 70 cm^3	16 (115 cm^3; 73–217 cm^3)	41

Table 2. TN categories in all patients.

Tabelle 2. Verteilung der TN-Stadien.

	N0	N1	N2	N3	Total
T1	1	0	4	0	5
T2	1	4	6	1	12
T3	0	1	2	1	4
T4	4	5	9	0	18
Total	6	10	21	2	39

customized bite block. CT images (2 mm slice thickness) were acquired from the top of vertex to the level of the carina.

The target volumes were drawn on each axial planning CT slice, based on diagnostic CT images, supplemented with fused diagnostic MRI and/or PET-CT scans. The gross tumor volume (GTV) included the gross extent of the primary disease and involved lymph nodes. PTV1 (planning target volume) was defined by adding a 0- to 15-mm margin to GTV, dependent on the GTV proximity to critical structures. PTV2 covered areas at high risk for potential microscopic disease. PTV3 included the clinically negative bilateral cervical lymphatics down to the supraclavicular fossae (elective PTV).

Organs at risk were outlined in three dimensions with an estimated planning organ-at-risk volume (PRV) margin of 2–10 mm.

We used an extended-field IMRT (EF-IMRT) technique, where the primary was treated in one phase along with the regional lymph nodes. Irradiation was delivered with five or seven coplanar beam angles by a 6-MV dynamic multileaf collimator (MLC) system (sliding-window technique; Varian Medical Systems, Palo Alto, CA, USA). Example of a five-field inverse plan is shown in Figure 1.

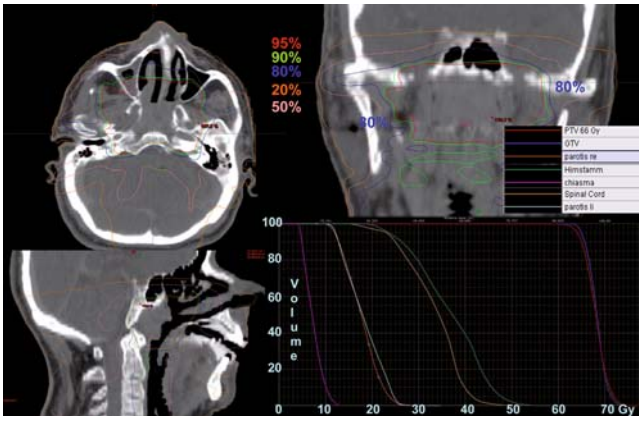

Figure 1. Isodose curves of a five-field inverse plan for a patient with T2 No (stage IIB) carcinoma of the nasopharynx displayed on the axial, coronal and sagittal planes through the primary tumor. Dose-volume histograms for the relevant structures.

Abbildung 1. Isodosenkurven von einem Fünf-Felder-Plan bei einem Patienten mit Nasopharynxkarzinom T2 No (Stadium IIB) durch den Primärtumor in axialer, koronarer und sagittaler Richtung. Dosis-Volumen-Histogramme für die relevanten Strukturen.

Prescription Dose

As previously described [33], SIB-IMRT was performed using the following schedules (five fractions/week each):

- SIB2.00: daily dose 2.00 Gy (PTV1)/1.70 Gy (PTV2)/1.54 Gy (PTV3); total dose: 70.00 Gy (n = 17);
- SIB2.11: daily dose 2.11 Gy (PTV1)/1.80 Gy (PTV2)/1.64 Gy (PTV3); total dose: 69.60 Gy (n = 19);
- SIB2.20: daily dose 2.20 Gy (PTV1)/2.00 Gy (PTV2)/1.80 Gy (PTV3); total dose: 66.00 Gy (n = 3).

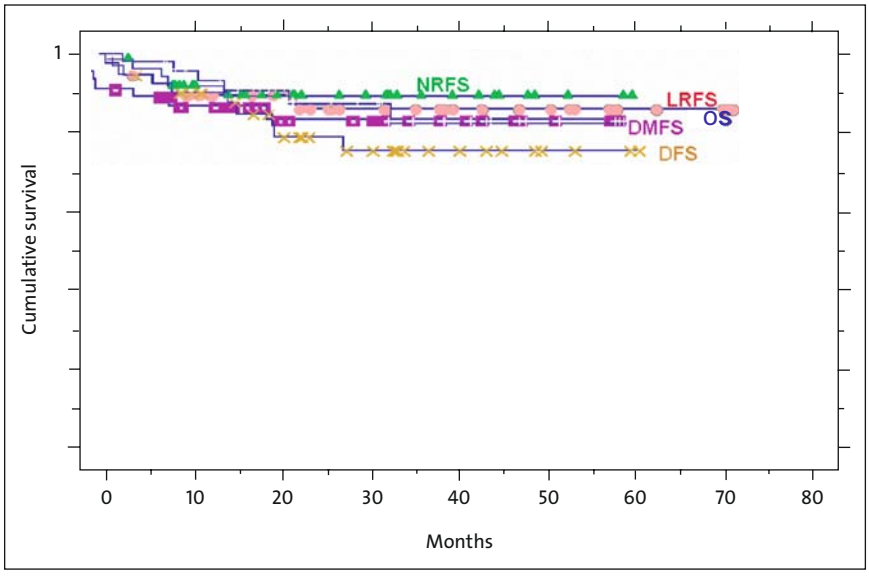

Figure 2. Kaplan-Meier estimate of actuarial 3-year local relapse-free survival (LRFS), nodal relapse-free survival (NRFS), distant metastases-free survival (DMFS), disease-free survival (DFS), and overall survival (OS).

Abbildung 2. Kaplan-Meier-Kurven des aktuarischen 3-Jahres-Überlebens in Bezug auf lokale Tumorkontrolle (LRFS), nodale Kontrolle (NRFS), fernmetastasenfreies Überleben (DMFS), krankheitsfreies Überleben (DFS) und Gesamtüberleben (OS).

The mean total treatment time was 46.7 days (33–58 days).

In cases with central nervous system involvement, the D_{max} accepted was 2.00 Gy (SIB2.00). The dose was normalized to the mean dose in PTV1. For intensity optimization the prescribed dose should encompass at least 95% of the PTV. No more than 20% of any PTV would receive > 110% of its prescribed dose, while no more than 1% of any PTV would receive < 93% of the desired dose.

Chemotherapy

All patients with stage II–IV disease (n = 38) received concurrent cisplatin (40 mg/m^2 i.v. weekly [n = 36] or 100 mg/m^2 i.v. on days 1, 22, and 43 [n = 2]) as well as three cycles of neoadjuvant/adjuvant chemotherapy with cisplatin (100 mg/m^2 i.v.) and 5-fluorouracil (1,000 mg/m^2 continuous i.v., days 1–4) every 4 weeks (n = 27; modified Head and Neck Intergroup protocol 0099) [1]. 30 of the patients who received weekly cisplatin

Table 3. Characteristics of failed patients (n = 8). AD: alive with disease; DOD: dead of disease; EBV: Epstein-Barr virus; IMRT: intensity-modulated radiotherapy; SIB: simultaneous integrated boost; tGTV: total gross tumor volume; WHO: World Health Organization.

Tabelle 3. Charakteristika der rezidivierten Patienten (n = 8). AD: Leben mit Erkrankung; DOD: Tod wegen Erkrankung; EBV: Epstein-Barr-Virus; IMRT: intensitätsmodulierte Radiotherapie; SIB: simultan integrierter Boost; tGTV: Gesamttumorvolumen; WHO: Weltgesundheitsorganisation.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
TNM stage	T2 N2 M0	T4 N1 M0	T1 N2 M0	T3 N2 M1	T4 N0 M0	T4 N2 M0	T1 N2 M0	T2 N1 M0
Stage grouping	III	IVA	III	IVC	IVA	IVA	III	IIB
WHO histology	Type 1	Type 1	Type 1	Type 3	Type 1	Type 1	Type 3	Type 1
Grading (G)	G3	G3	G3	G3	G3	G3	G2	G2
EBV status	–	NA	+	+	NA	+	+	NA
Gender	Female	Male	Male	Male	Male	Male	Male	Male
Ethnicity	Caucasian	Caucasian	Caucasian	Chinese	Caucasian	Caucasian	Caucasian	Caucasian
tGTV volume (cm^3)	22	163	92	35	85	121	21	144
IMRT scheme	SIB2.11	SIB2.11	SIB2.11	SIB2.11	SIB2.11	SIB2.00	SIB2.20	SIB2.11
Chemotherapy (cycles)								
• Concurrent	4	1	4	7	3	5	5	6
• Neoadjuvant/adjuvant	0	0	1/2	2/1	0	1/0	2/0	0
Local failure (months post treatment)	–	Persistence	–	–	5	–	22	Persistence
Nodal failure (months post treatment)	15	–	–	–	–	–	–	3
Distant metastases (months post treatment)	–	6	24	Initially M1	–	1	–	11
Outcome (months post treatment)	AD (24)	AD (24)	AD (31)	AD (47)	DOD (10)	DOD (39)	DOD (25)	DOD (17)

(77%) completed five to seven concurrent cycles. In patients in whom cisplatin was contraindicated, carboplatin was substituted (n = 3).

Follow-Up

Institutional standards for posttreatment patient assessment included physical examination with additional fiberoptic nasopharyncoscopy at the Department of Head and Neck Surgery approximately every 2 months in the 1st year of follow-up, every 3 months in the 2nd year, every 6 months in the 3rd–5th year, and annually thereafter. A baseline MRI scan of the nasopharynx and neck was obtained within 3–6 months. Suspected findings were specified with PET-CT and were histologically proven.

Normal-tissue effects were graded according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) radiation morbidity scoring criteria [10]. Xerostomia was subjectively assessed by the patients.

Statistical Analysis

Statistical calculations were performed using StatView® program (Abacus Concepts Inc., CA). p-values of ≤ 0.05 were considered statistically significant.

Results

Treatment Outcome and Patterns of Failure

Analysis was based on follow-up data available as of January 1, 2009. The median follow-up was 30 months (range: 8–71 months).

The actuarial 3-year local relapse-free, nodal relapse-free, distant metastases-free and disease-free rates were 86%, 89%, 85%, and 72%, respectively (Figure 2). The 3-year estimate of overall survival was 85%. At the time of analysis, 29 patients were alive with no evidence of disease (75%), four were alive with local and/or distant disease (10%), four died of disease (10%), and two died with intercurrent disease (5%; Table 3).

Prognostic Factors

Univariate analysis was performed to examine the impact of various prognostic factors. Differences in overall survival according to histology were statistically significant with worst prognosis in WHO type 1 [38] compared to WHO type 2/3 (75% vs. 93%; p = 0.03). There was also a trend in favor of WHO type 2/3 regarding local control (74% vs. 94%; p = 0.052).

Differences in 3-year local control rate according to T-stage were statistically significant, favoring T1/T2 lesions compared to T3/T4 (94% vs. 82%; p < 0.001).

Late Toxicity

There was no grade 4 late toxicity observed. The most common late effect was xerostomia. At the 12-month postirradiation follow-up, xerostomia grade 3 was assessed in three patients (8%), while five patients (13%) experienced xerostomia grade 2. At 24 months, grade 2 xerostomia was observed in four patients (10%). Grade 3 xerostomia insisted in two patients (5%), by whom the D_{50} values (dose delivered to 50% of the organ volume) to the right/left parotid was 40.6 Gy/49.8 Gy and 35.2 Gy/48.0 Gy, respectively.

Table 4. Dose-volume statistics of all patients derived from dose-volume histograms for gross tumor volume (GTV) and comparison to other series. NA: not assessable.

Tabelle 4. Dosis-Volumen-Statistiken von Dosis-Volumen-Histogrammen für das Tumorvolumen (GTV) im untersuchten Kollektiv und Vergleich mit anderen Serien. NA: nicht angebbar.

	GTV average (range)		
	Current study	**Lee et al. [22]**	**Poon et al. [28]**
Volume (cm^3)	70.0 (10.7–221.0)	104.0 (10.0–669.2)	121.9 (2.3–669.2)
Mean dose (Gy)	70.9 (67.7–73.0)	74.5 (63.3–94.6)	74.4 (69.4–77.3)
Maximum dose (Gy)	76.5 (70.8–81.5)	79.3 (65.8–93.8)	80.7 (74.1–87.5)
Minimum dose (Gy)	61.8 (48.7–69.4)	49.4 (16.2–71.5)	48.2 (33.1–69.5)
% volume receiving ≤ 95% of the prescribed dose	2.8 (0.0–19.3)	2.7 (0.0–93.0)	1.99 (0.0–6.1)
% volume receiving ≤ 90% of the prescribed dose	0.7 (0.0–11.0)	1.6 (0.0–66.0)	0.99 (0.0–4.1)
% volume receiving ≥ 105 of the prescribed dose	17.3 (0.0–72.9)	75.5 (0.0–99.0)	71.5 (40.3–91.2)
% volume receiving ≥ 107 of the prescribed dose	5.8 (0.0–56.6)	NA	NA

Table 5. Dose-volume statistics of all patients derived from dose-volume histograms for high-dose planning target volume (PTV) and comparison to other series. NA: not assessable.

Tabelle 5. Dosis-Volumen-Statistiken von Dosis-Volumen-Histogrammen (DVH) für Hoch-Dosis-Planungszielvolumen (PTV) im untersuchten Kollektiv und Vergleich mit anderen Serien. NA: nicht angebbar.

	High-dose PTV average (range)		
	Current study	**Poon et al. [28]**	**Palazzi et al. [27]**
Volume (cm^3)	252.3 (68.4–704.7)	424.32 (147.2–247.7)	246 (23–589)
Mean dose (Gy)	69.3 (65.5–71.8)	NA	70.5 (66.1–72.6)
Maximum dose (Gy)	77.8 (74.2–82.9)	79.8 (73.3–86.7)	NA
Minimum dose (Gy)	47.0 (18.5–60.0)	28.8 (12.8–60.4)	NA
% volume receiving ≤ 95% of the prescribed dose	9.7 (1.6–23.9)	3.4 (0.7–17.0)	5.5 (1.4–10)
% volume receiving ≤ 90% of the prescribed dose	2.0 (0.1–8.7)	2.2 (0.3–12.3)	NA
% volume receiving ≥ 105 of the prescribed dose	10.4 (0.8–37.7)	83.6 (62.3–96.4)	NA
% volume receiving ≥ 107 of the prescribed dose	3.6 (0.0–24.0)	NA	NA

One patient developed cisplatin-related (five cycles concurrently) grade 3 hearing loss. The D_{50}/D_{max} values to the right and left middle/inner ear of the patient were 38.1 Gy/56 Gy and 34.0 Gy/55 Gy, respectively. One patient with T4 N1 disease developed dysphagia grade 3, which still persisted at 24-month follow-up, when he also remained PEG-(percutaneous endoscopic gastrostomy-)dependent; in this case, the caudal border of PTV1 was at the level of the glottic larynx. One patient presented with positive Lhermitte's sign at the 12-month clinical evaluation that resolved 4 months later. The D_5 (dose delivered to 5% of the organ volume)/D_{10} (dose delivered to 10% of the organ volume) to the myelon PRV (myelon + 5- to 8-mm margin) were 42.7/39.6 Gy, respectively, while D_{mean}/D_{max} were 58.1/34.5 Gy.

In summary, persistent grade 3 late effects were observed in three patients (8%). There were no cases of temporal lobe necrosis, clinical optic neuropathy, osteoradionecrosis, severe soft-tissue fibrosis, or clinical hypopituitarism.

Dose-Volume Analysis

Tables 4 and 5 show the DVH statistics for the target volumes. The maximum and minimum doses are point doses. Compared to the corresponding values published by others (Table 4) [22, 28]), our GTV mean dose revealed to be ~ 3 Gy lower, while comparable nominal prescription dose was provided. The percentage of the GTV that received ≤ 95% of the prescribed dose remained equal. On the contrary, by the other series, the majority of the GTV received > 105% of the prescribed dose. This could raise a risk for lower tumor control in our cohort. However, there is no clear evidence for a loss of tumor control so far. Additionally, regarding optimal effective dose, there is a controversy in the optimal radiation dose, as, for example, in pediatric NPC, presenting mainly with WHO type 3 histology, it has been shown that radiation doses > 60 Gy appear necessary to achieve a high rate of locoregional control [41].

Table 6 shows the DVH statistics for the critical normal structures organized in series, while Table 7 outlines the DVH statistics for the normal tissues organized in parallel. Quantitative DVH analysis showed that there was significant sparing of the critical structures, a result that was consistent with the clinical observation of excellent treatment tolerance. DVH comparison of the normal structures organized in parallel showed lower dose values compared to that of Lee et al. [22], which may in part explain the low rate of important late effects in our own series.

Discussion

Disease Control

IMRT series with altered fractionation schemes report local control rates of 84–98% and overall survival rates of 74–92%. However, the local failure rate remains still > 10% in patients with T3/T4 tumors [7, 15, 16, 18, 22, 27, 40, 43].

In our study, the locoregional failure as well as disease-free survival and overall survival rates are in the range of

NPC IMRT series published so far (Table 8), despite the fact that our cohort includes predominantly patients of Caucasian origin (95%), with a consecutively higher percentage of patients with WHO type 1 histology (41%) and a relatively greater proportion of patients with stage IV disease (54%), except for the study by Kwong et al. (72%) [20].

Postfailure analysis of isodose plans showed that all local recurrences were located within the high-dose volume, suggesting that contoured PTVs and the immobilization system were adequate. The absence of local failure in cases with GTV volume < 16 cm^3 may suggest adequate dose for small tumors [34]. A more effective dose may be required for locally advanced disease. Considering the favorable tolerance profile in our cohort, a careful dose increase may be possible (besides of other theoretical ways to biologically increase effectivity [19, 23]).

All six patients with N0 status remained nodally controlled. As previously described [35], in spite of our rather restrictive elective PTV definition regarding level I, none of the nodal recurrences were located in level I. One has, however, to consider that there was effective dose in level Ib, even in cases where this level was not included in PTV (Table 9).

Evaluation of DVH analysis showed that our GTV DVH curves are slightly left-shifted compared to reported series [22, 27] (Table 4). Lee et al. [22] explained the tumor overdosage by the fact that the prescribed dose was the minimum dose that encompassed the tumor target volume. Our left shift raises a risk for lower tumor control. However, there is no clear evidence for a loss of tumor control so far.

Comparisons of high-dose PTV DVH values [27, 28] are difficult and of limited meaning, as there are no international standards of IMRT schedules and the nominal doses are delivered using different dose constraints with different dose calculations to different related PTV definitions between centers.

Toxicity

IMRT-chemotherapy was well tolerated (no grade 4 late complications). In comparison to Lee et al. [22], improved sparing of normal structures (parotid, temporomandibular joint, ear) in our study may in part explain the low rate of important late effects. As it has been

Table 6. Dose-volume statistics derived from dose-volume histograms for serial critical normal structures and comparison to the series by Lee et al. [22]. D_5: dose to 5% of volume; D_{10}: dose to 10% of volume; NA: not assessable.

Tabelle 6. Dosis-Volumen-Statistik von Dosis-Volumen-Histogrammen für serielle kritische Normalstrukturen im untersuchten Kollektiv und Vergleich mit der Serie von Lee et al. [22]. D_5: Dosis in 5% des Volumens; D_{10}: Dosis in 10% des Volumens; NA: nicht angebbar.

Organ[a]	Current study		Lee et al. [22]	
	D_5 (Gy) Average (range)	D_{10} (Gy) Average (range)	D_5 (Gy) Average (range)	D_{10} (Gy) Average (range)
Brain stem	47.7 (34.9–60.6)	45.2 (31.9–58.2)	46.3 (26.6–67.0)	43.5 (17.6–65.0)
Spinal cord	38.4 (33.3–47.0)	36.6 (30.6–45.2)	36.5 (9.8–46.3)	30.0 (1.9–45.7)
Chiasm	21.7 (2.4–62.7)	20.4 (1.9–61.4)	28.7 (3.6–55.7)	26.9 (3.5–54.0)
Temporal lobes	41.7 (22.5–67.1)	36.6 (10.0–65.0)	NA	NA
Optic nerves				
• Right	19.2 (2.2–52.9)	18.7 (1.5–50.9)	25.7 (8.0–67.7)	23.3 (2.9–65.8)
• Left	22.4 (2.0–72.3)	20.3 (1.5–71.0)	21.5 (7.5–61.8)	20.6 (7.5–62.0)

[a]All organs were outlined with an estimated margin of 2–10 mm in three dimensions.

Table 7. Dose-volume statistics derived from dose-volume histograms for parallel normal critical structures and comparison to the series by Lee et al. [22]. D_{50}: dose to 50% of volume; D_{80}: dose to 80% of volume; NA: not assessable; PTV: planning target volume; TMJ: temporomandibular joint.

Tabelle 7. Dosis-Volumen-Statistik von Dosis-Volumen-Histogrammen für parallele kritische Normalstrukturen im untersuchten Kollektiv und Vergleich zur Serie von Lee et al. [22]. D_{50}: Dosis in 50% des Volumens; D_{80}: Dosis in 80% des Volumens; NA: nicht angebbar; PTV: Planungszielvolumen; TMJ: Kiefergelenk.

Organ	Current study			Lee et al. [22]	
	Volume (cm^3) Average (range)	D_{50} (Gy) Average (range)	D_{80} (Gy) Average (range)	D_{50} (Gy) Average (range)	D_{80} (Gy) Average (range)
Parotid gland					
• Right	25.4 (13.8–41.4)	31.1 (17.5–68.2)	21.8 (13.6–59.6)	34.8 (7.9–72.3)	24.6 (5.5–67.7)
• Left	29.5 (25.7–46.6)	32.6 (21.2–69.3)	22.6 (13.0–67.8)	33.9 (13.4–60.0)	24.4 (6.2–52.8)
Parotid outside PTV				NA	NA
• Right	15.2 (5.0–32.1)	24.3 (16.8–49.6)	19.5 (13.3–46.6)		
• Left	14.6 (0.2–36.6)	24.4 (17.8–46.0)	19.7 (11.9–41.0)		
TMJ					
• Right		36.7 (13.4–64.6)	30.9 (11.4–60.1)	49.0 (19.4–79.0)	44.3 (16.5–78.2)
• Left		36.9 (23.7–64.4)	30.7 (17.5–55.0)	49.5 (24.9–78.3)	43.1 (21.1–74.0)
Ear					
• Right		41.4 (21.9–69.9)	35.3 (19.3–68.3)	49.5 (12.8–74.4)	42.4 (8.8–72.0)
• Left		44.9 (24.8–68.4)	38.2 (20.3–61.7)	48.7 (20.2–64.3)	42.9 (12.5–60.6)

Table 8. Results from selected series treating NPC with intensity-modulated radiotherapy (IMRT) ± chemotherapy (Chemo). DFS: disease-free survival; DMFS: distant metastases-free survival; FU: follow-up; fx: fraction; LC: local control; MSKCC: Memorial Sloan-Kettering Cancer Center; NA: not assessable; OS: overall survival; RC: regional control; UCSF: University of California, San Francisco; WHO: World Health Organization.

Tabelle 8. Resultate ausgewählter Publikationen zur intensitätsmodulierten Radiotherapie (IMRT) ± Chemotherapie (Chemo) bei Patienten mit Nasopharynxkarzinom. DFS: krankheitsfreies Überleben; DMFS: fernmetastasenfreies Überleben; FU: Verlaufsbeobachtung; fx: Fraktion; LC: lokale Tumorkontrolle; MSKCC: Memorial Sloan-Kettering Cancer Center; NA: nicht angebbar; RC: nodale Kontrolle; OS: Gesamtüberleben; UCSF: University of California, San Francisco; WHO: Weltgesundheitsorganisation.

Study	Patients (n)	Inclusion period (median FU)	WHO type 1 (%)	Caucasians (%)	Stage III/IV (%)	Chemo (%)	Dose total (Gy)/fx	Time point (year)	LC (%)	RC (%)	DMFS (%)	DFS (%)	OS (%)	Grade 4 late toxicity (%)
Kam et al., 2003 [18] (Hong Kong)	63	2000–2002 (29 months)	0	0	57	30	66/2[a]	3	92	98	79	NA	90	0
Bucci et al., 2004 [4] (UCSF)	118	1995–2003 (30 months)	NA	18	74	90	69.9/2.11	4	96	98	72	NA	74	8
Chong et al., 2004 [8] (China)	118	2001–2004 (19 months)	0	0	50	NA	70/2.33	3	98	NA	88	NA	86	7
Wolden et al., 2006 [40] (MSKCC)	74	1998–2004 (35 months)	5	68	77	93	70.2/2.34	3	91	93	78	67	83	0
Kwong et al., 2006 [20] (Hong Kong)	50	2000–2004 (25 months)	0	0	100	68	70/2	2	94	95	94	93	92	8
Fang et al., 2008 [12] (Taiwan)	110	2002–2004 (40 months)	2	0	53	57	70.2–75.6/1.8	3	84	84	83	NA	85	NA
0225 RTOG, 2008 [21] (USA)	68	2003–2005 (24 months)	NA	54	59	NA	70/2.12	2	92	90	86	73	79	0
Present study	39	2002–2008 (30 months)	41	95	85	97	69.9/2.11	3	86	89	85	72	85	0

[a]After IMRT, brachytherapy (4 × 3 Gy) or conformal boost (4 × 2 Gy) was delivered additionally

estimated that parotid tolerance is likely a stepwise function [11], our results could suggest that achievement of dose reduction at any dose level may improve the probability of parotid function.

The compliance rate to chemotherapy was similar to other IMRT studies [4, 8, 12, 20, 22, 40], as 69% of our patients completed the chemotherapy regimen protocol. In the Intergroup trial [1], this number reached the proportion of only 55% in the adjuvant part, with the most frequently mentioned reason for noncompliance the refusal by the patient to undergo additional treatment and/or toxicity. A high level of compliance to chemotherapy seems important, as it has been suggested the addition of chemotherapy confers more benefit for WHO type 1 tumors than for type 3 tumors [30].

Conclusion

The somewhat lower dose delivered to the high-dose PTV in our non-Asian NPC patients, presenting with less radioresponsive WHO type 1 histology and predominantly advanced stage, did not translate into a clearly lower disease control, while likely related to the very satisfactory treatment tolerance. As a consequence of the somewhat lower DVH values resulting from our IMRT dose specification, we changed the standardization of our internal IMRT dose constraints toward some higher GTV dosage by normalizing to the GTV (100% prescription of the isodose should surround GTV + 0–5 mm, resulting in a mean PTV GTV of ~ 103%), while the 95% isodoses should still surround the other PTVs.

Table 9. Coverage of level Ib lymph nodes (n = 78; two levels Ib/patient).

Tabelle 9. Dosierung der Lymphabflussregion Ib (n = 78), zwei Levels Ib/Patient).

	Nodal status n (%)	Ib contoured > 50 Gy	> 45 Gy	30–45 Gy	< 30 Gy
N0	23 (30)	0	0	5	18
N+	55 (70)	24	24	20	11

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